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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/327,761	06/07/1999	DONALD W. PETERSEN	99.501	5876

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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/327,761	PETERSEN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,12-21 and 35-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,12-21 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Initially Applicants are requested to note that the Examiner for this application has changed, future correspondence should be directed to Allison Ford, Art Unit 1651, whose contact information can be found below.

For purposes of clarity, the most recent prosecution history of this application is briefly summarized:

Claims 2, 3, 12-21 and 35-38 are pending in the current application.

All claims were finally rejected in an office action mailed 15 December 2004 under 35 USC 103(a) as being obvious over the teachings of O'Leary et al (US Patent 5,484,601), Yim et al (US Patent 5,385,887) and Gertzman et al (US Patent 6,030,635), taken as a whole.

Applicants appealed the rejection to the Board of Patent Appeals and Interferences on 11 July 2005.

The Examiner's Answer, mailed 20 September 2005, added a new grounds of obviousness-type double patenting rejection over the claims, in light of the claims of US Patent 6,652,887 and the claims of US Application Nos. 09/947,833 and 10/060,697. Applicants noted the new grounds of rejection in the Reply Brief received 21 November 2005.

The Board of Patent Appeals and Interferences provided a decision on 7 December 2006 (Appeal No. 2006-0766). The Examiner was affirmed in part. The Board affirmed the obviousness-type double patenting rejections, but reversed the sole obviousness rejection.

In light of the Board decision, Applicants have requested reconsideration of the application. This request, received 29 January 2007, is granted; the finality of the rejections of record is withdrawn; however new grounds of rejection have been set forth below. 37 CFR 1.198 provides that when a decision by the Board of Patent Appeals and Interferences on appeal has become final for judicial review, prosecution of the proceeding before the primary examiner

will not be reopened or reconsidered by the primary examiner except under the provisions of § 1.114 or § 41.50 of this title without the written authority of the Director, and then only for the consideration of matters not already adjudicated, sufficient cause being shown. MPEP 1214.03 states that if the examiner has specific knowledge of the existence of a particular reference or references which indicate non-patentability of any of the appealed claims as to which the examiner was reversed, he or she should submit the matter to the Technology Center (TC) Director for authorization to reopen prosecution under 37 CFR 1.198 for the purpose of entering the new rejection. Claims 2, 3, 12-21 and 35-38 have been considered on the merits. The TC Director's approval is indicated at the end of this action reopening prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' claim 19 is found indefinite because it lacks antecedent basis for the limitation "the plasticizing substance" in the 3rd line of the claim. Parent claim 2 recites a cellulose derivative, not the more generic term 'plasticizing substance.' Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 12-20 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary et al (US Patent 5,484,601), in view of Yim et al (US Patent 5,385,887), Sottosanti (US Patent 5,366,507), Hanker et al (US Patent 4,619,655), Snyders, Jr (US Patent 5,425,769) and Wironen et al (WO 98/40113).

Applicants' claims are directed to a bone graft substitute composition that generally comprises (a) calcium sulfate; (b) a mixing solution; (c) a cellulose derivative; and (d) demineralized bone matrix. Some claims further define the specific mixing solution, the cellulose derivative, and the calcium sulfate (specifically as calcium sulfate hemihydrate), and the proportion (w/w) of each component. Applicants also include claims to a method of making a bone graft substitute composition, comprising combining the above described components.

At the time the invention was made, numerous bone graft substitute materials were known in the art. One such bone graft substitute material is described by O'Leary et al. Specifically O'Leary et al disclose a 'flowable' demineralized bone powder composition, comprising demineralized bone powder and a biocompatible liquid synthetic organic material as a carrier (which applicants call a mixing solution); optionally, thixotropic agents, medicaments and the like can further be included (See O'Leary et al, col. 1, ln 36-43). The bone powder is preferably provided in an amount equaling from about 5 to about 80 weight percent, more preferably from about 20 to about 60 weight percent (See O'Leary et al, col. 4, ln 18-22). O'Leary et al disclose glycerol as being a preferred carrier/suspension liquid; however, they further state that due to the natural tendency of the demineralized bone powder to separate when provided in glycerol, it is desirable to include thickeners (thixotropic agents), including carboxy methylcellulose (which applicants calls both a cellulose derivative and a plasticizing substance),

to improve the suspension-keeping characteristics of the composition (See O'Leary et al, col. 3, ln 55-col. 4, ln 6).

O'Leary et al further discloses methods of producing the bone composition, comprising combining the demineralized bone powder, with or without any of the recited optional ingredients such as the thickeners, with the biocompatible liquid synthetic organic carrier material (See O'Leary et al, col. 3, ln 15-20). It is noted that O'Leary et al defines 'flowable' as a consistency ranging from 'readily deformable' (e.g. putty-like) to 'runny' (See O'Leary et al col. 3, ln 30-36); thus the bone graft substitute material of O'Leary et al can be formed into, and provided as, a putty.

Therefore, O'Leary et al. provides the disclosure to produce a bone graft substitute composition containing a demineralized bone powder, a thixotropic agent, such as carboxymethyl cellulose (which is a cellulose derivative), and a mixing solution. O'Leary teaches that this bone graft substitute may be prepared in multiple forms from liquid to paste-like depending upon the requirements of the practitioner. O'Leary et al does not disclose the inclusion of calcium sulfate in their bone graft substitute composition.

However, while O'Leary et al do not include calcium sulfate in their bone graft composition, it would have been obvious to one of ordinary skill in the art to add calcium sulfate to the bone graft substitute composition of O'Leary et al because, at the time the invention was made, calcium sulfate was known to be a beneficial and useful component in bone grafting materials, for example, see Yim et al: Yim et al disclose a bone substitute material useful for delivering osteogenic proteins comprising calcium sulfate hemihydrate and cellulose materials, including cellulose derivatives. Yim et al report the calcium sulfate hemihydrate improves osteoconduction, and improves the moldability of the material (See Yim et al, col. 7, ln 50-65). The cellulose derivatives, which include carboxymethyl cellulose, aid in sequestering the proteins at the implant site so as to enhance their effectiveness (See Yim et al, col. 7, ln 26-49).

Additionally, at the time the invention was made, the use of both calcium sulfate and demineralized bone matrix together in bone grafting materials was known, see Sottosanti, Hanker et al, and Snyder, Jr: Sottosanti et al disclose a bone graft composite material comprising demineralized, freeze-dried, allogenic bone (DFDBA) and calcium sulfate (See Sottosanti et al, col. 2, ln 24-26); Hanker et al disclose mixing demineralized freeze-dried bone with Plaster of Paris (from calcium sulfate hemihydrate) (See Hanker et al, col. 2, ln 24-25); and Snyders, Jr disclose a composition comprising collagen, plaster (from calcium sulfate hemihydrate + sterile water), and demineralized bone matrix as having osteoinductive capabilities (See Snyders, Jr, col. 3, ln 51-54; col. 4, ln 1-5; and col. 5, ln 42-43).

Based on the abundance of teachings in the art regarding the benefits of calcium sulfate, both individually and in combination with demineralized bone matrix, in bone grafting compositions, it would have been obvious to one of ordinary skill in the art to include calcium sulfate in the composition of O'Leary et al. Additionally, though not explicitly stated, because calcium sulfate hemihydrate is naturally a powder, it would be necessary to add an aqueous solvent to the bone grafting material in order to hydrate and activate the calcium sulfate to a workable consistency; one of ordinary skill in the art would be aware such a solution would be necessary and the selection and use of either sterile water or saline or other buffers is deemed conventional and well within the skill of the practitioner (thus a mixing solution would inherently be recognized as necessary, and thus provided, in any bone graft composition comprising calcium sulfate).

While the previous rejections of record have relied on the idea that "combination of two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose" is *prima facie* obvious (see *In re Kerkhoven,* 626 F.2d 846, 205 USPQ 1069 (CCPA 1980)) as the motivation for adding

calcium sulfate to the composition of O'Leary et al, motivation can alternatively be found in the teachings of the prior art: It is noted the composition of O'Leary et al preferably comprises glycerol as a carrier material; however, at the time the invention was made the suitability of glycerol as the carrier matrix/material in the bone substitute material of O'Leary et al (material marketed as GRAFTON®) was questioned. In reviewing GRAFTON®, Wironen et al note that because glycerol is water soluble, it was considered likely that the glycerol (along with the demineralized bone powder) would prematurely wash away from the implantation site (See Wironen et al, Page 3). In view of this concern, one of ordinary skill in the art would have been motivated to utilize calcium sulfate as a carrier/scaffold material in the material of O'Leary et al in place of the glycerol, as calcium sulfate was recognized as a mechanically strong (i.e. does not wash away in presence of body fluid), yet totally resorbable material that is particularly suited for use in bone substitute materials (See Snyders, Jr, col. 4, ln 57-68). Calcium sulfate is resorbed by the body in a period of approximately 4-20 weeks, which approximately correlates with the time period for new bone formation. Clearly, resorption of the scaffold material at a rate approximately equal to that of new bone formation is desirable, as it would permit natural bone regeneration on the natural timescale. One would have a reasonable expectation of successfully including the calcium sulfate hemihydrate as a scaffold/carrier material for the bone graft substitute material of O'Leary et al because use of calcium sulfate in combination with the bone graft material of O'Leary et al, because use of both calcium sulfate (including calcium sulfate hemihydrate) and demineralized bone matrix in a single grafting material was well established in the art (See Sottosanti, Hanker et al, & Snyder, Jr).

The inclusion of calcium sulfate hemihydrate within the composition of O'Leary et al would result in a bone graft substitute composition comprising demineralized bone matrix, a

cellulose derivative, specifically carboxymethylcellulose, calcium sulfate hemihydrate, and mixing solutions, comprising glycerol and/or sterile water, saline or other appropriate buffers.

With regards to the exact concentrations of each component, it is noted that O'Leary et al does suggest providing bone powder in an amount between about 20 to about 60 weight percent (See O'Leary et al, col. 4, ln 18-22); with regards to the amount of calcium sulfate, cellulose material, and mixing solution to be included, optimization of these amounts is deemed to be well within the skill of the practitioner at the time the invention was made as it is clear that the amount of calcium sulfate is directly related to desired rate of set up of the composition, i.e. the more calcium sulfate used, the faster the composition will set up and harden (See Snyder, Jr, col. 4, ln 61-64). Further, since the amount of water that is needed to hydrate any given amount of calcium sulfate hemihydrate is known, it is well within the skill of the practitioner to infer that the amount of mixing solution present is inversely related to the desired set up time and directly proportional to the ultimate consistency of the composition, i.e. the less mixing solution used, the less dilute the calcium sulfate and the faster the set up time of the composition. As a result, the composition will be more paste-like in consistency. The amount of cellulose material will likewise affect the final viscosity, as it functions as a thickening agent, or alternatively can be manipulated based on the presence or absence of proteins, as it is known to function as a protein sequestering agent (See Yim et al). See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). While it is noted that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation, as evidenced above, the prior art recognizes the results produced by the claimed components and teaches ranges of the claimed ingredients that overlap the claimed ranges. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 3, and 12-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary et al (US Patent 5,484,601), in view of Yim et al (US Patent 5,385,887), Sottosanti (US Patent 5,366,507), Hanker et al (US Patent 4,619,655), Snyders, Jr(US Patent 5,425,769) and Wironen et al (WO 98/40113), and further in view of Gertzman et al (US Patent 6,030,635).

Applicants' claims are directed to a bone graft substitute composition that generally comprises (a) calcium sulfate; (b) a mixing solution; (c) a cellulose derivative; and (d) demineralized bone matrix. Some claims further define the specific mixing solution, the cellulose derivative, and the calcium sulfate (specifically as calcium sulfate hemihydrate), and the proportion (w/w) of each component. Dependent claim 21 requires the bone graft composition to further comprise a bone allograft.

The teachings of O'Leary et al are set forth above. It has been established that though the composition of O'Leary et al does not comprise calcium sulfate hemihydrate, inclusion of such would have been obvious to the person of ordinary skill in the art at the time the invention was made.

It is further noted O'Leary et al does not teach the presence of allograft bone in the bone substitute composition. However, at the time the invention was made, inclusion of allograft bone in the composition of O'Leary et al, as modified to further comprise calcium sulfate hemihydrate, as above, would have been obvious to the person of ordinary skill in the art in view of the teachings of Gertzman et al. Gertzman et al. teaches another malleable paste bone graft substitute composition for filling bone defects. In the Background of the Invention, Gertzman et al discloses various substances that are known to be included in a bone growth promoting

composition. Included in this list is autologous bone, bone marrow, blood, calcium sulfate, and allograft bone. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further include allograft bone in the composition of O'Leary as modified to include calcium sulfate hemihydrate. One of ordinary skill in the art would have been motivated to include the allograft bone in order to maximize the bone growth promoting activity of the composition for the expected benefit of the addition of the "building blocks" of new bone, i.e. collagen fiber reinforced hydroxyapatite matrix containing active bone morphogenic proteins at an area in need thereof. One of ordinary skill in the art would have had a reasonable expectation of success since the composition of Gertzman is structurally and functionally similar to the composition of O'Leary. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

With regards to the obviousness-type double patenting rejection: is noted Applicants have submitted acceptable terminal disclaimers against each of the commonly owned US Patents or patent applications, and thus the rejections/provisional rejections are withdrawn.

With regards to the obviousness rejection: The arguments of Applicants provided in the Appeal Brief of 11 July 2005, which were affirmed by the Board of Patent Appeals and Interferences, were based on the idea that one of ordinary skill in the art would not have been motivated to add calcium sulfate (as disclosed by Yim et al) to the composition of O'Leary et al in order to improve handling, moldability or consistency properties of the composition of O'Leary et al. It was set forth that because O'Leary et al does not suggest their composition

suffers from poor handling, moldability, or consistency, and because it is not clear from the disclosure of Yim et al that calcium sulfate hemihydrate is even capable of imparting such properties to any composition, motivation based on such is inappropriate and does not support a *prima facie* case of obviousness.

The arguments and opinion of the Board have been fully considered, and in light of such, the rejection of record has been modified. However, the claims stand rejected under the idea that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to add a calcium sulfate component, particularly calcium sulfate hemihydrate, to the composition of O'Leary et al. The new grounds of rejection attempts to better explain the state of the art, and the knowledge of the artisan in the field of bone grafting and tissue engineering, as such must be taken into consideration in determining obviousness, See *Graham v. John Deere Co.* 383 US 1, 17-18, 148 USPQ 459, 467 (1966) & *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). As set forth in the rejection above, numerous bone grafting composition materials were known in the art, certain components were generally known to be routinely used due to their known osteoconductive and/or osteoinductive properties, including both demineralized bone matrix and calcium sulfate (See, e.g., Sottosanti, Hanker et al, Snyders, Jr, and Gertzman et al). When the full scope of teachings of the prior art is taken into consideration, it is clear that calcium sulfate is not merely just a 'set-up agent' that affects handling, consistency and moldability of a composition, but rather was recognized as an osteoconductive material. For example, Snyder et al discloses calcium sulfate "not only does not inhibit the normal growth and healing process of bone, it also has been characterized as an accelerant of the same because of its contribution of calcium ions to the process [of bone growth and healing]." (Snyders, col. 4, ln 64-68); in fact, each of the cited references recognize the osteoconductive properties of calcium sulfate. Therefore, one of ordinary skill in the art would have been motivated to add calcium sulfate to the composition of O'Leary et al, not because the potential effect on set-up time, but

rather in order to improve the osteoconductive properties of the final bone graft substitute material.

Furthermore, while improving the osteoconductive properties of the final material is considered, by itself, to be sufficient motivation to add calcium sulfate to the O'Leary et al composition, it has been further set forth that at the time the invention was made certain deficiencies were noted in the composition of O'Leary et al, specifically the poor ability of the glycerol carrier solution to retain the demineralized bone at the implant site, use of a calcium sulfate carrier material would overcome this deficiency as calcium sulfate degrades at a rate approximately equal to that of new bone formation. Thus, one would be further motivated to utilized calcium sulfate in the composition of O'Leary et al in order to correct for the recognized deficiency associated with the glycerol carrier material.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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